# Cytogenetic Studies in Ovarian Cancer

**Jacqueline Whang-Peng, Turid Knutsen, Edwin C. Douglass, Elizabeth Chu, Robert F. Ozols, W. Michael Hogan, and Robert C. Young**

**ABSTRACT:** *Cytogenetic studies of ovarian cancer have been conducted in the Medicine Branch, NCI, National Institutes of Health for 5 years. A total of 72 patients were studied by direct preparation and/or 1- to 3-day short-term culture of ascites (86 samples), pleural fluid (4 samples), and tumor (2 samples). Repeat examinations (1–24 months later) were performed in 7 of the 72 patients. Forty-four patients (62%) were successfully analyzed with banding techniques: 6 patients had adenocarcinoma, 7 had serous adenocarcinoma, 13 had serous papillary adenocarcinoma, 7 had serous papillary cystadenocarcinoma, 2 had mucinous adenocarcinoma, 6 had undifferentiated or poorly differentiated adenocarcinoma, 1 had clear cell adenocarcinoma, and 2 were not classified. Of these 44 patients, 29 had received prior chemotherapy, 14 were untreated, and in 1 patient the treatment status was unknown. Aneuploidy was observed in all patients and there was considerable variation in the chromosome numbers (even within single samples), often ranging from diploidy to triploidy to tetraploidy. All 44 patients had numerical abnormalities and 39 had structural abnormalities. The chromosomes most frequently involved in structural abnormalities (in decreasing order according to the number of patients involved) were #1, #3, #2, #4, #9, #10, #15, #19, #6, and #11; the least involved chromosomes were #21 and #5. Clone formation and the number of chromosomes involved in structural abnormalities increased with duration of disease and were more extensive in patients treated with chemotherapy than in patients treated with surgery alone. Our data did not show a deletion of chromosome #6 (6q−) to be specific for ovarian cancer.*

## INTRODUCTION

Ovarian cancer is the leading cause of gynecologic cancer death in the United States. In most cytogenetic investigations of this cancer, the type studied has been epithelial carcinoma of the ovary, which accounts for 80%–90% of ovarian malignancies. Studies conducted both prior to and since the development of chromosomal banding techniques have shown multiple structural changes associated with ovarian cancer [1–12], and several of these investigations have revealed no specific chromosomal marker [4–6]. In 1979, however, Trent and Salmon [9], using the agar colony system, reported a specific nonrandom chromosomal abnormality in their ovarian cancer patients, a deletion of the long arm of chromosome #6 (6q−), which previously had not been observed. A year later, Wake et al. [10] reported the same marker plus an additional specific marker involving chromosome #14 in their

From the Cytogenetic Oncology Section, Medicine Branch, Clinical Oncology Program, Division of Cancer Treatment; and the Cytopathology Section, Laboratoy of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD.

*Address requests for reprints to Dr. Jacqueline Whang-Peng, National Cancer Institute, NIH, Building 10, Room 12N226, Bethesda, MD 20205.*

*Received July 1, 1982; accepted March 14, 1983.*



© 1984 by Elsevier Science Publishing Co., Inc.
52 Vanderbilt Ave., New York, NY 10017

Cancer Genetics and Cytogenetics 11, 91–106 (1984)
0165-4608/84/$03.00

study of papillary serous adenocarcinoma of the ovary. During the 5-year period, 1976 to 1981, we have had the opportunity to study 72 ovarian cancer patients. We were interested in identifying any specific markers and the degree to which chromosomal abnormalities were influenced by duration of the disease, prognosis, and treatment.

## MATERIALS AND METHODS

### Materials

Cytogenetic studies of ovarian cancer were conducted in the Medicine Branch, NCI, of the National Institutes of Health from June 1976 until April 1981. A total of 72 patients were studied by direct preparation and/or 1–3-day culture of ascites (86 samples), pleural fluid (4 samples), and tumor (2 samples). Repeat examinations were performed in 7 patients, 1–24 months later. Successful banding preparations were obtained in 44 patients from 45 ascites samples and 3 pleural fluid samples.

### Pathology and Cytology

The diagnosis was established from pathologic examination of the surgical specimen when possible. Cytologic determinations were performed on 5–15 ml of fluid. The cells were collected on a Millipore filter, fixed with modified Carnoy's (a 70% solution of 95% alcohol, 25% chloroform, and 5% acetic acid), and stained according to the method of Papanicolaou [13].

### Cytogenetic Studies

Ascites and pleural fluid specimens were collected with heparin, the specimen was centrifuged, and the cell button resuspended in either a colcemid solution (direct preparation) or in McCoy's 5A medium with 20% fetal calf serum (1–3-day culture). The cells were harvested according to the air-dried chromosome technique of Tjio and Whang [14]. Tumor samples were minced, and the cells dissociated from fibrous tissue by the use of a steel mesh; the cells collected were resuspended in media at a final concentration of $10^6$/cc. Chromosome preparations were made directly or after 1–3 days of culture. In all cases, 1 slide was subjected to regular Giemsa staining, 1–2 slides were saved for C-banding if necessary, and the remaining slides were Giemsa-trypsin banded [15]. Karyotypic analysis was performed according to the conventions established at the Paris Conference of 1971 [16].

### Ploidy Designations

The ploidy designations used in this article are defined as follows: hypodiploidy, fewer than 46 chromosomes per cell; pseudodiploidy, 46 chromosomes with an abnormal karyotype; hyperdiploidy, 47–59 chromosomes; triploidy, 60–80 chromosomes; and tetraploidy, 81–120 chromosomes.

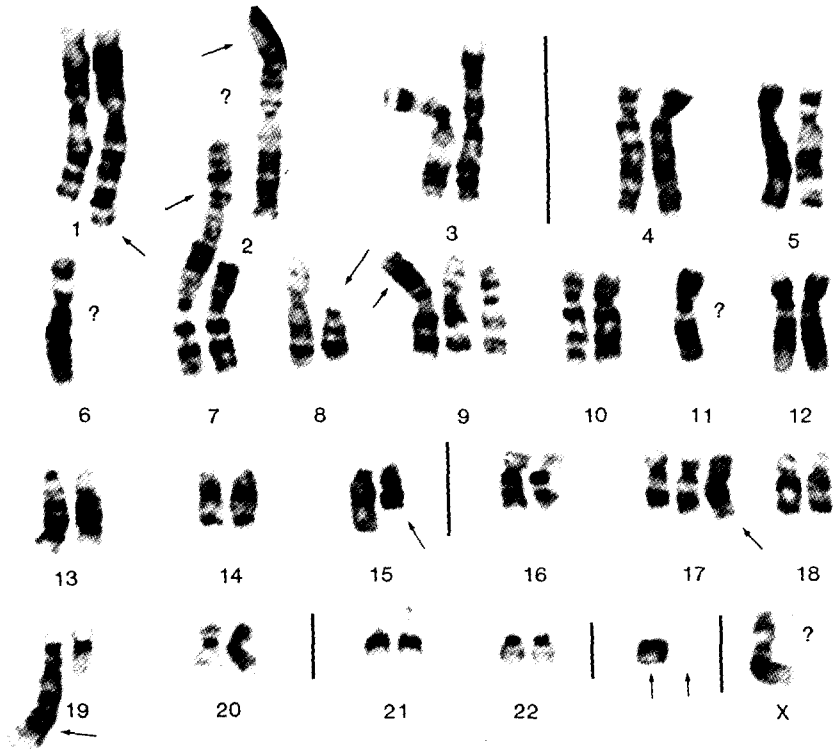
## RESULTS

Successful banding analysis was obtained in 44 patients, who were divided into the following histologic types according to their pathologic and/or cytologic diagnoses: adenocarcinoma (6 patients); serous tumor (27 patients), including serous adenocarcinoma (7 patients), papillary serous adenocarcinoma (13 patients), and papil-

lary serous cystadenocarcinoma (7 patients); mucinous cystadenocarcinoma (2 patients); undifferentiated or poorly differentiated adenocarcinoma (6 patients); and clear cell adenocarcinoma (1 patient). Two patients were not classified.

Successful banding preparations were obtained from 45 ascites and 3 pleural fluid specimens from the 44 patients. All patients showed aneuploidy with numerical abnormalities and 39 patients had structural chromosomal abnormalities. Figures 1–4 show karyotypes from four patients with various structural abnormalities. There was considerable variation in cell chromosome number including wide ranges within single samples: hypodiploidy only (5 patients); hyperdiploidy only (2 patients); hypodiploidy and pseudodiploidy (1 patient); pseudodiploidy, hyperdiploidy, and triploidy (1 patient); hypodiploidy and hyperdiploidy (11 patients); hyperdiploidy and triploidy or tetraploidy (16 patients); and triploidy and/or tetraploidy (8 patients). Table 1 shows the clonal abnormalities in the 29 patients with structural clonal abnormalities. All chromosome pairs were involved in structural abnormalities in these 44 patients, and the frequency of involvement (i.e., the number of patients involved per chromosome) is shown in Figure 5; chromosome #1 was the most commonly involved, followed by #3, #2, #9, #10, #15, #4, #19, #6, and #11, and chromosomes #21 and #5 were the least involved. Thirty patients had structural abnormalities of chromosome #1, and in 22 of these patients, the abnormality was clonal in nature. The most frequent abnormality of the short arm was 1p+, with the extra material of known or unknown origin; in the long

**Figure 1** Karyotype from case 19 showing: 46,X−X,−2,−6,−11,1q+,2p+,t(2;7), 8p11−, +9p+,15q23−,+17q+,19q+,+ring,+min.



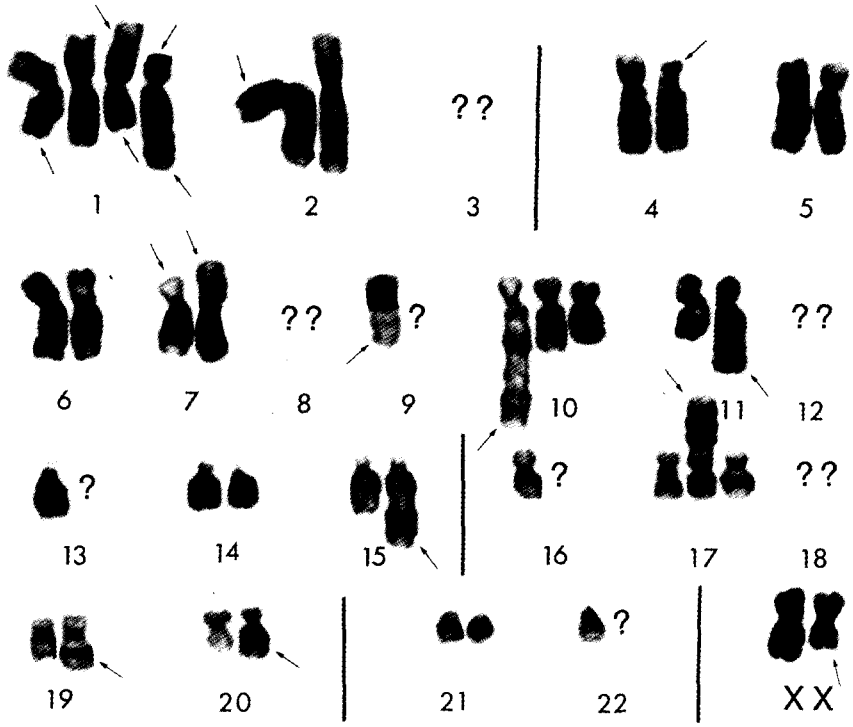



**Figure 2** Karyotype from case 26 showing: 38,XXq23−,−3,−3,−8,−8,−9,−12,−12,−13,−16,−18,−18,−22, 1q41−,1p+q32−,1p31−q+,2p+,4p15−,7p15−,7p+,9q−,t(1q;10), 11q+,15q+,17p+,19q+,20q+.

arm, deletion of the band area q21 to q32 was the most common. Table 2 shows the variety of abnormalities of chromosome #1 seen in these patients and Figure 6 shows the abnormalities seen in ≥50% of the cells in each affected patient.

Chromosome #3 abnormalities were seen in 27 patients, the abnormalities being clonal in 16 of these patients. The number of patients and the percentage of cells involved for each specific abnormality are listed in Table 3. The most common abnormality was 3p12− (7 patients), followed by 3p25− and 3p13−; 3p+ and 3q+ were each observed in 5 patients.

Chromosome #6 abnormalities were present in 17 patients (Table 4); in 9 patients they were clonal. Six of the 17 patients had deletions involving the p22 band in 8%–80% of their cells; deletions involving bands 6q25, 6q23, and 6q24 were also noted. Five patients had structural abnormalities of chromosome #6 in 50% or more of their cells (Figure 7). Fifteen patients had chromosome #14 abnormalities, which were clonal in 6 patients. The most common abnormalities were 14q+, t(14;15), and t(13;14), and the number of cells involved ranged from 11%–60% (Table 5.) A translocation between the terminal portion of the long arm of chromosome #14 (14qter) and chromosome #6 was not observed in any of the 44 patients.

Patient 6 had chromosome numbers ranging from 38 to 85 per cell, and all cells had a homogeneously staining region (HSR) on the short arm of chromosome #7. At the time the specimen was collected, this patient had received no treatment whatsoever, including surgery. Patient 31 had chromosome numbers ranging from

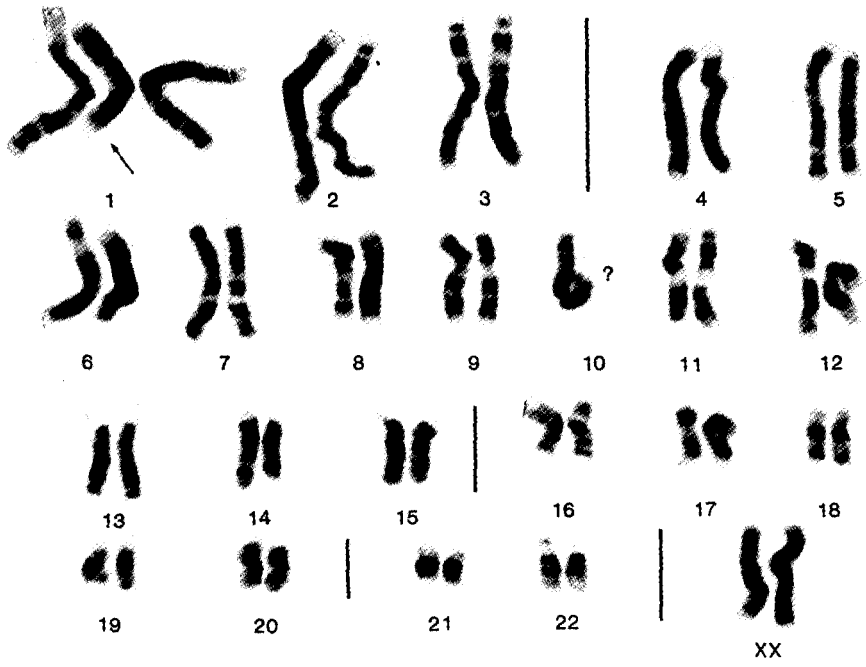



**Figure 3** Karyotype from case 27 showing: 46,XX, −10, +1q41−.

**Figure 4** Karyotype from case 40 showing mutiple numerical and structural abnormalities (see Table 1).

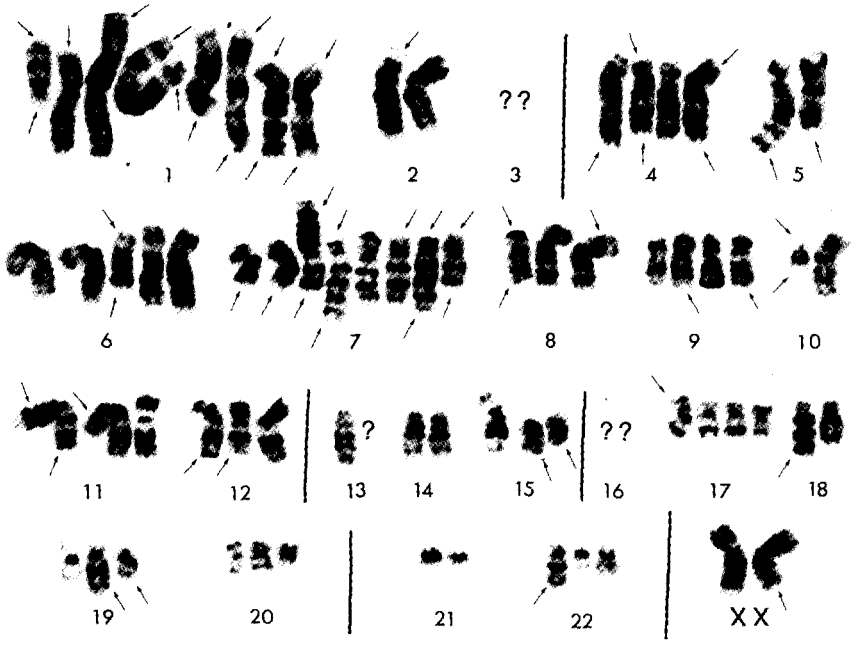


**Table 1** Structural clonal abnormalities in ovarian cancer (29 patients)

| Patient no. | Diagnosis | Survival (months) | Chromosome[a] no. (modal) | No. of cells[b] Tot(nl) | Clonal structural abnormalities |
|---|---|---|---|---|---|
| 1 | Adeno. | 12 | 60–82 (64) | 2(0) | 1q21−; t(2q;3p); 10p12−; 15q+ |
| 2 | Pap. adeno. | 12 | 46–128 (61) | 12(1) | dic(1;3); 1q21−; 2p12−; 3p11−; 3q+; dic(10;D); 12p+; dic(13;19); t(14;15); 19q+; 22q12−; Xq+ |
| 4 | Pap. cystadeno. | 3 | 38–85 (38;76) | 6(0) | 1p+(Xp); 4q+; 9p+; t(13;14); 16q+; 19q+ |
| 6 | Pap. cystadeno. | 6 | 56–78 (74) | 6(1) | 1p+(3p21-29); 3p21−; 3p21−q21−; 4q+; dic(6;22)(p22→qter::q13→pter); HSR on 7p; t(10;11); dup(11q); t(11;13); t(18;19) |
| 8 | Adeno. | 15 | 40–174 (64) | 4(0) | 1q+; 2q+; 19q+ |
| 9 | Pap. cystadeno. | 13 | 37–46 (39;46) | 6(0) | 1p+; 2q+; 4p11− |
| 11 | Pap. adeno. | 30 | 41–107 (56) | 6(0) | 3p11−q12; 3q12−; t(4;19)(q22→qter::q13→qter); 11p+; 15q21−; −X |
| 12 | Adeno. | 27+ | 38–47 (41) | 4(0) | 1p+(1q41-44); 3p12−q21−; 10q23−; 11q+; 19q+ |
| 13 | Serous adeno. | 17 | 62–polypl (64;130) | 2(0) | 1p+(3q21-29); 11q+(4q); 22q11−; Xq23− |
| 14 | Adeno. | 23+ | 72–87 (75) | 2(0) | 6p14− |
| 15 | Adeno. | | 69–81 (74) | 5(0) | 1p+(3p22-26); Xq23− |
| 16 | Adeno. | 14 | 32–60 (35) | 2(0) | 1q21−; t(1p;11q); 20q+ |
| 18 | Poorly diff. | 16 | 32–125 (59) | 7(0) | 1q31−; 3p12−q21−; 3q11−; 10q25−; 12p+; 19q+; 20q+; 22q13− |
| 19 | Pap. adeno. | 16 | 28–86 (44) | 14(0) | 1q+; dic(2;7); 11p+; ring; min |
| 22 | Pap. adeno. | 16 | 43–88 (44;88) | 3(0) | 1q32−; 4q+; 6q23− |
| 25 | Pap. adeno. | 14 | 42–91 (60) | 8(0) | 3p24−q24−; 6q+; 13q+; 19q+; 20q+ |
| 26 | Pap. adeno. | 14 | 19–86 (43;86) | 13(0) | 1q32−; 2p+; 3p21−q13−; 3p+q+; 3p13−; t(7q;12q); 10p13−q+; 10p+q+; 11q+; 11p+; 12p+; 15q+; 17p+; 17q11−; 19q+; 20q+; several unclass. |
| 29 | Adeno. | 10 | 35–octopl (38;75) | 11(1) | t(2;11)(q37;q11); 3p13−; 3p12−; t(3q;9q); t(3;6)(p24;p23); 6q21−; 7p13−; 7p+; 9q21−; 19q+(18q12-33) |

| | | | | | |
|---|---|---|---|---|---|
| 31 | Mucinous adeno. | 3 | 31–octopl (64) | 14(1) | i(1q); 10q22−; i(15q); min |
| 32 | Pap. cytsadeno. | 10 | 57–196 (84) | 2(0) | 10q+; min |
| 33 | Pap. adeno. | 33 | 45–105 (57) | 8(0) | dic(1;7)(q12→pter::q12→pter); 1q11−; del(3)(p14-23); 3p23−q21−; 3p11-q24−; 7q+; dic(8;17); 9q+; dic(9;20); 10q+; dup(13)(q13→21); 16p+; 16q+; 19q+; 20q+ |
| 35 | Adeno. | 10 | 37–48 (44) | 9(0) | 1p+(1q23-44)q12−; 1p36−q+(1q31-42); 2q+; t(3q;1q;1q34−); 3p22−q25−; 4q+; 16q+; t(1;16)(q23;q24); 20q+ |
| 36 | Adeno. | 18+ | 39–130 (56) | 5(0) | 2p11−; 3p21−; 4p13−; 6p22−; 8q+; 13q+; 19q+; 20q+ |
| 37 | Serous adeno. | 37 | 47–32ploid (68) | 3(0) | dic lp+(21); 9q+; 10p12−; 20q+; 22q12− |
| 38 | Pap. adeno. | 23 | 30–16ploid (36;72) | 5(0) | 1q31−; 3p12−; 9p+; 11p+; t(13;14); 20q+ |
| 40 | Pap. cystadeno. | 27 | 50–134 (72) | 12(0) | 1q22−; 1p11−; 1p+(3q21-29); 1p+(3q21-29)q22−; 1q32−; 2p+; 3p14−; 3q+; 3p+; 3p13−; 5q+; 6q24−; 7p21−; 8q21−; 9q+; 9q31−; 10q25−; 11p+; 11q+; 12q+; t(13;14); t(13;15); 17q+; 18q+; 19q+; 20q+; i(22q); Xq22− |
| 41 | Poorly diff. | 22 | 46–88 (79) | 8(2) | 6q22−; 19q+; 22q12−; min; small acro |
| 42 | Clear cell adeno. | 4 | 27–158 (44;87) | 9(2) | 1p31−; 1q31−; 3q+; 3p+; 3p12−q21−; 5q+; 9p+; 11p+; 12q+; t(14;15); small acro |
| 44[d] | Adeno. | 16 | 55–16ploid (71–74) | 22(0) | 1p+(q31-44)q25−; 1q+(22-31); dup(2)(q22-31); t(11;4;3p24-26); t(4q;4q;11q); 6q23−; 10q21−; 11p+; dic(11p;1p;1q); 12p+; t(13;15); t(14;14); t(14;15); 20q+; Xq21− |

[a]Based on combined total of banded and unbanded cells.

[b]Banded karyotype.

[c]No survival data available.

[d]Patient 44: combined results of 4 specimens.

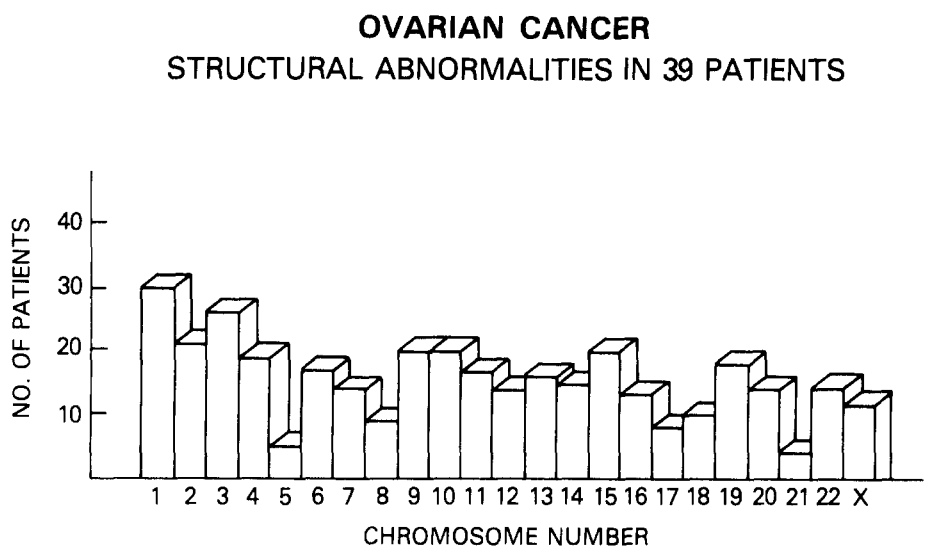



**Figure 5** Incidence of structural abnormalities in 39 patients.

60 to 67 and multiple double minutes (DMs) in 1 cell and one DM in 4 additional cells. This patient had been treated surgically but had no history of chemotherapy or radiotherapy. Patient 32, who had been treated with PAC (platinum, adriamycin, and cytoxan), had 4 DMs in a single cell.

The patients were divided into two groups on the basis of treatment history (Table 6). One group (29 patients) had received chemotherapy and/or radiotherapy, and the other group (14 patients) had received no such treatment (most patients in both groups had received surgical treatment; the treatment status was unknown in 1 patient). In the untreated group, the number of chromosomes involved in structural abnormalities in each patient ranged from 0 to 16, with a median of 3. In the treated group, the number of chromosomes involved ranged from 0 to 22, with a median of 9 chromosomes. Five of the 14 untreated patients and 23 of the 29 treated patients showed evidence of clone formation.

Table 7 shows a comparison between the number of chromosomes involved in structural abnormalities per patient during the first 2 months of disease and the 2 months immediately preceding death. The former group had a median number of 2.5 chromosomes involved and 4 of these 10 patients had clone formation. There were 11 patients in the group studied 2 months prior to death, 8 of whom had clone formation, and the median number of chromosomes involved was 8. No increase in chromosomal breakage or aberrations was observed in this group of patients when the results were compared to those of a normal control group.

## DISCUSSION

Specific chromosomal markers had not been reported in ovarian cancer until 1979, when Trent and Salmon proposed that there is an association between ovarian adenocarcinoma and deletion of part of the long arm of chromosome #6; this proposition was based on their studies using the agar colony culture method [9]. The same year, Woods et al. [8] published their studies on tissue culture lines established from four patients with serous cystadenocarcinoma of the ovary: chromo-

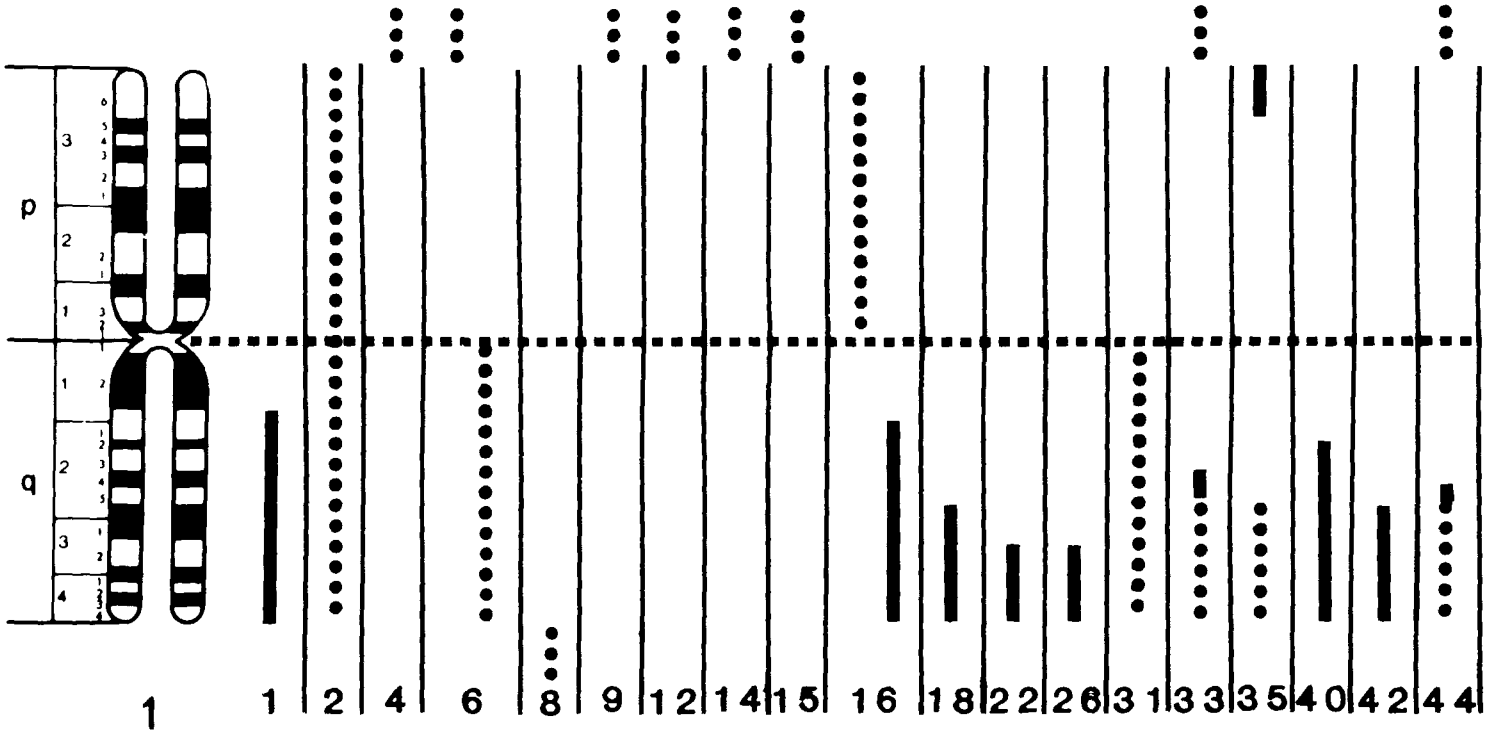



**Figure 6** Chromosome #1 abnormalities in ovarian cancer in ≥50% of cells per specimen. Solid lines represent deletions, dots represent translocations, and numbers at bottom represent patient numbers.

**Table 2** Structural abnormalities of chromosome #1 in ovarian cancer

| Abnormalities | Number of patients | Percent cells |
|---|---|---|
| Short arm (p) | | |
| I. Deletions | | |
| 1p11 – | 3 | 8%–21% |
| 1p12 – | 1 | 7% |
| 1p21 – | 1 | 8% |
| 1p22 – | 1 | 7% |
| 1p31 – | 1 | 60% |
| 1p32 – | 4 | 10%–25% |
| 1p34 – | 1 | 20% |
| 1p35 – | 1 | 25% |
| 1p36 – | 1 | 8% |
| II. Translocations to 1p (1p+) | | |
| 1p+(undetermined origin) | 2 | 67%–100% |
| 1p+(dup 1p) | 1 | 8% |
| 1p+(2q22-37) | 1 | 7% |
| 1p+(3) | 1 | 100% |
| 1p+(3q21-29) | 3 | 50%–100% |
| 1p+(3p22-26) | 1 | 100% |
| 1p+(12q) | 1 | 17% |
| dic 1p+(21) | 1 | 67% |
| dic 1p+(Xp) | 1 | 83% |
| III. Translocations | | |
| t(1p;7q) | 1 | 13% |
| t(1p;9) | 1 | 10% |
| t(1;10)(p34;q21-26) | 1 | 13% |
| t(1p;16q) | 1 | 13% |
| t(1p22-44;17) | 1 | 20% |
| IV. Other abnormalities | | |
| i(1p) | 2 | 9%–50% |
| Long arm (q) | | |
| I. Deletions | | |
| 1q11 – | 4 | 7%–25% |
| 1q12 – | 3 | 8%–20% |
| 1q13 – | 1 | 20% |
| 1q21 – | 7 | 10%–100% |
| 1q22 – | 4 | 13% |
| 1q31 – | 6 | 8%–43% |
| 1q32 – | 6 | 14%–100% |
| 1q41 – | 3 | 8%–14% |
| 1q42 – | 2 | 13%–50% |
| II. Transolcations to 1q (1q+) | | |
| 1q+(origin undetermined) | 5 | 7%–50% |
| 1q(dup) | 1 | 14% |
| 1q+(dup1q22-31) | 2 | 25%–100% |
| i(1q) | 2 | 7%–64% |
| III. Translocations of 1q to other chromosomes | | |
| t(1q;2p) | 1 | 33% |
| dic(1q;4) | 1 | 17% |
| t(1q22-44;4p) | 1 | 17% |
| t(1q21-41;7p) | 1 | 20% |
| t(1q;9p) | 1 | 10% |
| t(1q;12p) | 1 | 10% |
| Short arm (p) and long arm (q) involvement | | |
| I. Involvement of chromosome 1 only | | |
| 1p32-q31 – | 1 | 20% |
| 1p32-q32 – | 1 | 20% |
| 1p36-q25 – | 1 | 7% |
| 1p36-q+(?1q31-42) | 1 | 67% |
| 1p+(1q22-44) | 1 | 50% |
| 1p+(1q41-44) | 2 | 50%–100% |
| 1p+q22 – | 1 | 29% |
| 1p+q32 – | 1 | 14% |
| 1p+q41 – | 1 | 8% |
| 1p+(1q23-33)q12 – | 1 | 33% |
| 1p+(1q31-34)q25 – | 1 | 100% |
| 1p+(1q31-44)q41 – | 1 | 14% |
| 1p+(q) | 1 | 20% |
| II. Translocations to chromosome 1 from other chromosomes | | |
| dic(1;7)(q12→pter::q12→pter) | 1 | 87% |
| dic(11p;1p;1qdup22→31) | 1 | 100% |

**Table 3** Structural abnormalities of chromosome #3 in ovarian cancer (27/44 patients, 16 clonal)

| Abnormalities | No. of patients | Percent cells |
|---|---|---|
| p Arm | | |
| 3p+ | 5 | 8%–33% |
| 3p11− | 1 | 36% |
| 3p12− | 7 | 8%–100% |
| 3p13− | 4 | 14%–70% |
| inv(3p13) | 1 | 25% |
| del(3)(p14p21) | 1 | 25% |
| del(3)(p13p23) | 1 | 25% |
| del(3)(p13p24) | 1 | 20% |
| 3p14− | 1 | 50% |
| 3p21− | 3 | 14%–80% |
| 3p22− | 2 | 25%–33% |
| 3p23− | 1 | 13% |
| 3p25− | 5 | 8%–100% |
| t(2q;3p) | 1 | 100% |
| dic(3p;7) | 1 | 7% |
| t(11;4;3p24-26) | 1 | 77% |
| q Arm | | |
| 3q+ | 5 | 50%–80% |
| 3q11− | 1 | 29% |
| 3q12− | 1 | 67% |
| 3q13− | 1 | 14% |
| 3q21− | 1 | 17% |
| 3q24− | 1 | 50% |
| 3q26− | 1 | 25% |
| 3q27− | 1 | 8% |
| t(3q;1q;1q34) | 1 | 22% |
| t(1p;3q) | 1 | 14% |
| t(3q;9q) | 1 | 20% |
| t(3q;10;11) | 1 | 8% |
| t(3;6)(q24;q23) | 1 | 80% |
| p and q arm involvement | | |
| I. Involvement of chromosome 3 only | | |
| 3p11−q12− | 2 | 14%–83% |
| 3p11−q27− | 1 | 38% |
| 3p12−q21− | 3 | 29%–57% |
| 3p12−q22− | 2 | 20%–50% |
| 3p13−q21− | 2 | 10%–11% |
| 3p13−q22− | 1 | 33% |
| 3p13−q23− | 1 | 14% |
| 3p14−q21− | 2 | 14%–17% |
| 3p14−23q21− | 1 | 25% |
| 3p21−q13− | 1 | 100% |
| 3p21−q21− | 4 | 8%–80% |
| 3p21−q26− | 1 | 11% |
| 3p21−q+ | 1 | 25% |
| 3p21−q23− | 1 | 100% |
| 3p22−q21− | 1 | 8% |
| 3p22−q22− | 1 | 13% |
| 3p22−q25− | 1 | 22% |
| 3p22−q+ | 2 | 13% |
| 3p23−q21− | 2 | 25% |
| 3p23−q+ | 2 | 13%–25% |
| 3p24−q24− | 1 | 25% |
| 3p25−q21− | 1 | 14% |
| 3p25−q26− | 1 | 11% |
| 3p−q+ | 1 | 8% |
| 3p+q21− | 1 | 13% |
| II. Translocations involving other chromosomes | | |
| dic(1;3) | 1 | 100% |
| tricen(22;3p;3q23;22) | 1 | 100% |

**Table 4** Structural abnormalities of chromosome #6 in ovarian cancer (17 patients, 9 clonal)

| | No. of patients | Percent cells |
|---|---|---|
| 6p+q25− | 1 | 10% |
| 6p11− | 1 | 8% |
| 6p22− | 5 | 9%–100% |
| dic(6;22)(p22→qter::q13→qter) | 1 | 80% |
| 6p25− | 1 | 8% |
| 6q21− | 3 | 17%–50% |
| 6q22− | 3 | 10%–66% |
| 6q23− | 2 | 33%–67% |
| t(3;6)(q24;q23) | 1 | 80% |
| 6q24− | 3 | 10%–25% |
| 6q25− | 5 | 8%–90% |
| 6q26− | 1 | 17% |
| 6q+ | 3 | 10%–25% |

some banding studies revealed that chromosome #6 was one of four chromosomes (#1, #3, #6, and #7) involved in markers in all four cell lines; chromosomes #2, #4, #5, #9, #11, and #15 were involved in markers in three of the cell lines.

In an article published in 1980, Wake et al. [10] reported the cytogenetic findings in short-term (2-day) cultures of 12 papillary serous adenocarcinomas of the ovary (5 primary tumors and 7 metastatic tumors or effusions). The two most frequent markers were 6q− and 14q+; both coexisted in 8 cases. In 6 of these cases, markers

**Figure 7** Chromosome #6 abnormalities in ovarian cancer in ≥50% of cells per specimen. Solid lines represent deletions, dots represent translocations, and numbers at bottom represent patient numbers.

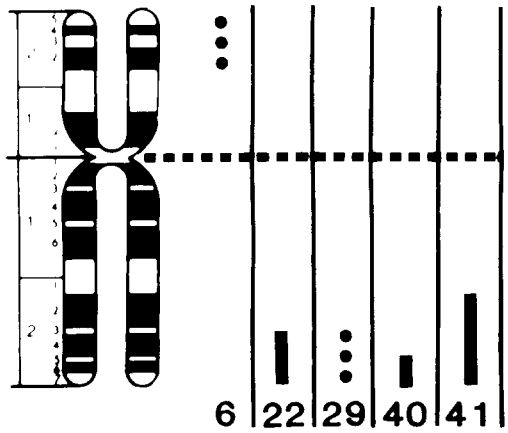


**Table 5** Structural abnormalities of chromosome #14 in ovarian cancer (15 patients, 6 clonal)

| | No. of patients | Percent cells |
|---|---|---|
| 14q+ | 6 | 11%–50% |
| i(14) | 1 | 17% |
| t(11q;14q) | 1 | 25% |
| t(13;14) | 5 | 14%–60% |
| t(14;14) | 1 | 41% |
| t(14;15) | 6 | 13%–45% |
| dic(14;22) | 2 | 7%–33% |

**Table 6** Ovarian cancer: Number of chromosomes involved in structural abnormalities per patient

Unknown status (1 patient)
4
Untreated (14 patients)
0, 0, 0, 0, 0, 1, 2[a], 4[a], 4, 8[b], 10[b], 15[b], 16[b], 16[b]
Treated (29 patients)
0, 1, 1, 2, 4, 4, 5[b], 5[b], 5[b], 5[b], 7[b], 8[b], 8[b], 8[b], 9[a], 9[b], 11[b], 11[b], 11[b], 11[b], 12[b], 13[b], 13[b], 14[b], 14[b], 17[b], 17[b], 18[b], 22[b]

[a]Median.

[b]Clone present.

were the result of a reciprocal translocation between the 2 [t(6;14)(q21;q24)]; in the other 2 cases with both markers, there was no evidence that chromosome #6 was the origin of the material translocated onto chromosome #14. The remaining 4 cases had either 6q− or 14q+. In a study of ovarian cancer from 3 different sites in one individual, Kusyk et al. [11] also found a 6q− marker (6q13−) as well as 11 other consistent markers, including 3 derived from chromosome #1. In our 44 cases, only 17 patients had abnormalities of chromosome #6 (ranking ninth to tenth; see Fig. 5), and only 12 of these showed a deletion of the q arm. Of the 3 patients showing 6q21−, none had this abnormality in 50% or more of their cells, and of the 13 patients with serous papillary cystadenocarcinoma, only 2 had clonal deletions of 6q (6q23− and 6q24−) while 3 patients had deletions of 6q in only one cell each. Fifteen patients in this series had abnormalities of chromosome #14 and 6 of these 15 had 14q+. In no case could the material translocated to chromosome #14 be identified as coming from chromosome #6, and most translocations involved D- and G-group chromosomes. Our data show no specific markers for ovarian cancer, including no evidence of a 6q deletion. In a recent discussion of the 6q−, Trent noted that they had observed this same marker in melanoma cells grown in the same agar colony system as had been used for their ovarian studies (personal communication). This marker may be an artifact produced by in vitro selection in the agar feeder layer procedure or absence of this marker in our series could be a result of the fact that we did not study primary tumor samples. However,

**Table 7** Ovarian cancer: Number of chromosomes involved in structural abnormalities

| | |
|---|---|
| Patients studied within 2 months of diagnosis | |
| Total patients | 10 |
| Patients with clone | 4 |
| Number of chromosomes affected per patient | |
| 0, 0, 0, 0, 2, 3[a], 8[a,b], 10[b], 15[b], 16[b] | |
| Patients studied within 2 months of death | |
| Total patients | 11 |
| Patients with clone | 8 |
| Number of chromosomes affected per patient | |
| 0[a], 1[a], 3, 7[a,b], 8[a,b], 8[a,b], 10[a,b], 10[a,b], 12[a,b], 15[a,b], 16[b] | |

[a]Chemotherapy.

[b]Clone.

markers of this type have more of a tendency to remain than to disappear, as the karyotype becomes increasingly complex in metastatic tissue.

Chromosome #1 abnormalities appear to be the most common cytogenetic abnormality in ovarian cancer and have been reported in over 80% of the cases studied by chromosome banding [5–11]. This is certainly true in the present study, where abnormalities of chromosome #1 were seen in 30/44 patients. The most common abnormality in these 30 patients was 1p+, which was seen in 16 patients, 10 of whom had it in 50% or more of their cells. The source of the extra material translocated to 1p were chromosomes #1 (5 cases), #2 (1 case), #3 (5 cases), #7 (1 case), #12 (1 case), #21 (1 case), and the X chromosome (1 case) (Table 1); one patient had two different 1p+ markers. In two cases, the origin of the translocated material was unknown. The second most frequent site of chromosome #1 abnormalities was the long arm region containing bands 21–44: 12 patients had deletions or translocations of this area in 50% or more of their cells.

Involvement of the long arm of chromosome #1 has frequently been emphasized in human malignancies, specifically regions 1q25-32 in hematologic disorders [17], 1q23-25 in myeloproliferative diseases [18], and 1q21-25 in breast and colonic cancer [19,20]. Abnormalities of chromosome #1 have also been reported in melanoma [21], Burkitt's lymphoma [22], and small cell lung cancer [23]. Combining this information with our own data, it appears that the long arm of chromosome #1 at band q21 or distal to it, whether duplicated or missing, may be somehow involved in neoplastic transformation. The other chromosomes most frequently involved in structural abnormalities were (in order of the number of patients) #3, #2, #9, #10, #15, #4, #19, #6, and #11; the chromosomes least involved were #5 and #21.

Homogeneously staining regions (HSR) and double minutes (DM) are seen more frequently in tissue culture than in direct or short-term cultured specimens. Trent and Salmon [10] noted either HSR or DM in 20% of their agar cultures of ovarian cancer cells, and all four of Wood's [8] lines had DM in 6%–31% of the cells; one cell line had a marker chromosome with a possible HSR. DMs (4–117/cell) were seen in all metaphases of a direct preparation of ascites from an untreated ovarian cancer patient reported by Olinici [2]. In the present study, one patient (case 6) had HSR on the short arm of chromosome #7 (7p) in 100% of her cells; DMs were noted in 2 patients, 1 untreated and 1 treated with PAC. HSRs and DMs are presently of great interest, particularly in regard to the study of drug resistance. They are

thought to represent areas of gene amplification [24, 25] in response to drug exposure. Only one of our three patients with HSRs or DMs had received any chemotherapy. The mechanisms for these phenomena remain unexplained at present.

Our findings indicate a correlation between treatment, disease duration, and the extent of chromosomal abnormalities in ovarian cancer. We noted an increase in the number of chromosomes involved in structural abnormalities in patients who had received chemotherapy: in 13 untreated patients, the median number of such chromosomes was 3 (range 0–16), while in the 29 treated patients the median was 9 (range 0–22). An increase in the number of structural abnormalities was also observed to occur with progress of the disease. In those patients studied within 2 months of diagnosis, the median was 2 chromosomes involved in structural abnormalities versus a median of 8 chromosomes involved within 2 months of death.

In summary, the results of our cytogenetic study of 44 patients showed that all had aneuploidy with extensive and complex numerical and structural abnormalities. Chromosome #1 was most frequently involved in structural abnormalities, but no specific abnormality was observed in the tumor cells of these patients. The degree of structural abnormalities correlated with both treatment and duration of the disease.

## REFERENCES


1. Arias-Bernal L, Jones HW (1968): Chromosomes of a malignant ovarian teratoma. Am J Obstet Gynecol 100, 785–789.
2. Olinici CD (1971): Double minute chromatin bodies in a case of ovarian ascitic carcinoma. Br J Cancer 25, 350–353.
3. Pogosyanz ME, Chudina AP, Rodkina RA (1972): Karyotypic changes in human ovarian cancers. Prob Oncol 18, 3–9.
4. Atkin NB, Baker MC, Robinson R, Gaze SE (1974): Chromosome studies on 14 near-diploid carcinomas of the ovary. Eur J Cancer 10, 143–146.
5. Tiepolo L, Zuffardi O (1973): Identification of normal and abnormal chromosomes in tumor cells. Cytogenet Cell Genet 12, 8–16.
6. Kakati S, Hayata I, Oshimura M, Sandberg AA (1975): Chromosomes and causation of human cancer and leukemia. X. Banding patterns in cancerous effusions. Cancer 36, 1729–1738.
7. Freedman RS, Pihl E, Kusyk C, Gallager HS, Rutledge F (1978): Characterization of an ovarian carcinoma cell line. Cancer 42, 2352–2359.
8. Woods LK, Morgan RT, Quinn LA, Moore GE, Semple TU, Stedman KE (1979): Comparison of four new cell lines from patients with adenocarcinoma of the ovary. Cancer Res 39, 4449–4459.
9. Trent JM, Salmon SE (1979): Karyotypic analysis of human ovarian carcinoma cells cloned in agar. Am J Human Genet 31, 379 (abstr).
10. Wake N, Hreshchyshyn MM, Piver SM, Matsui S, Sandberg AA (1980): Specific cytogenetic changes in ovarian cancer involving chromosomes 6 and 14. Cancer Res 40, 4512–4518.
11. Kusyk CJ, Seski JC, Medlin WV, Edwards CL (1981): Progressive chromosome changes associated with different sites of one ovarian carcinoma. J Natl Cancer Inst 66, 1021–1025.
12. Atkin NB, Baker MC (1981): Specific chromosome change in ovarian cancer. Cancer Genet Cytogenet 3, 275–276.
13. Papanicolaou GN (1954): Atlas of Exfoliative Cytology. Harvard University Press, Cambridge.
14. Tjio JH, Whang J (1962): Chromosome preparations of bone marrow cells without prior in vitro culture or in vivo colchicine administration. Stain Technol 37, 17–20.
15. Seabright MA (1971): A rapid banding technique for human chromosomes. Lancet 2: 971–972.

16. Paris Conference 1971 (1972): Standardization in human cytogenetics. Birth Defects 8, 7.
17. Rowley JD (1978): Abnormalities of chromosome no. 1 in haematological malignancies. Lancet 1, 554–555.
18. Gahrton G, Friberg K, Zech L, Lindsten J (1978): Duplication of part of chromosome no. 1 in myeloproliferative diseases. Lancet 1, 96–97.
19. Cruciger QVJ, Pathak S, Cailleau R (1976): Human breast carcinoma: Marker chromosomes involving 1q in seven cases. Cytogenet Cell Genet 17, 231–235.
20. Kovacs G (1978): Abnormalities of chromosome no. 1 in haematological malignancies. Lancet 1, 554.
21. Quinn LA, Woods LK, Merrick SB, Arabasz NM, Moore GE (1977): Cytogenetic analysis of twelve human malignant melanoma cell lines. J Natl Cancer Inst 59, 301–307.
22. Douglass EC, Magrath IT, Lee EC, Whang-Peng J (1980): Cytogenetic studies in non-African Burkitt's lymphoma. Blood 55, 148–155.
23. Whang-Peng J, Bunn PA, Kao-Shan CS, Lee EC, Carney DN, Gazdar AF, Minna JD (1982): A non-random chromosomal abnormality, del 3p(14-23), in human small cell cancer (SCLC). Cancer Genet Cytogenet 6, 119–134.
24. Biedler J, Spengler BA (1977): Metaphase chromosome anomaly: Association with drug resistance and cell-specific products. Science 191, 185–187.
25. Schimke RT, Alt FW, Kellems RE, Kaufman RJ, Bertinoa JR (1977): Amplification of dihydrofolate reductase genes in methotrexate-resistant culture mouse cells. Cold Spring Harbor Symp Quant Biol 42 (part 2), 649–657.